

ANIMAL MODEL OF HUMAN DISEASE

Inherited Copper Toxicosis in Bedlington Terriers

Wilson's Disease (Hepatolenticular Degeneration)

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Biologic Features

Wilson's disease is an inherited copper-loading disease of man leading to hepatic cirrhosis and degeneration of the lenticular nuclei and other areas of the brain if the patient is not treated. Although it was once thought that these patients absorbed more copper than normal from their food, the defect is now believed to be an inability to excrete copper into the bile, the main route for the disposal of copper by mammals. Copper accumulates in the liver and kidney, altering the former grossly and the latter more subtly. Eventually the copper starts accumulating in the brain and the cornea. The latter is evident as greenish rings, the Kayser-Fleischer rings. The early symptoms of excess brain copper are commonly misinterpreted as neurotic problems and are not clearly recognized until gross motor disturbances develop. As with so many inherited diseases of man, early diagnosis is usually not made in the first affected child in a family.

In 1975 Hardy and associates¹ reported an hereditary hepatic cirrhosis in Bedlington terriers in Minnesota. When copper stains were found to be strongly positive on slices of hepatic tissue, copper assays were done. In three Bedlington terrier livers the copper concentrations exceeded 200 μg /fresh tissue.

Although the first dogs with this copper-loading disease were older animals that died of hepatic failure associated with ascites, two other types of the disease were soon recognized.² Young adult dogs sometimes died after a 2- or 3-day fulminant illness that began with some stressful experience such as whelping, air shipment, or being exhibited at a dog show. The third course is an asymptomatic one, although there is laboratory evidence of the disease, including elevated serum SGPT and elevated hepatic copper.

After reviewing biochemical and histologic data on 144 Bedlington terriers scattered about the United States, Hardy and Stevens³ concluded that about two-thirds of the 6000 or 8000 Bedlington terriers in this country are affected by the copper-loading problem.

Normal dogs have an unusually high concentration of copper in their livers, about 200 μg /g dry weight. For comparison, normal human livers contain less than 35 μg /g dry weight. Affected Bedlington terriers begin to accumulate copper in their livers early in life. Concentrations over 10,000 μg /g may be reached⁴ when the dogs are 4 to 8 years old, following which there tends to be a slow fall. Cirrhotic changes develop years after hepatic copper has reached its peak level.^{5,6}

There are 4 grades of abnormality in the dog's liver as the disease progresses:^{5,6} pigment granules, mild focal hepatitis, periportal hepatitis resembling chronic active hepatitis, and finally cirrhosis. Curiously, hepatic iron is also elevated, some 4-fold, and is sequestered in small clusters of hepatocytes and macrophages ("iron granulomas").⁶

The excess copper is not in the cytosol but is in the sedimentable particles of the liver.⁴ The copper is in electron-dense granules in lysosomes,⁶⁻⁸ probably lipolysosomes⁶ (Figure 1).

Comparison With Human Disease

Inheritance is by autosomal recessive means in both.⁹ The hepatic accumulation of copper has the

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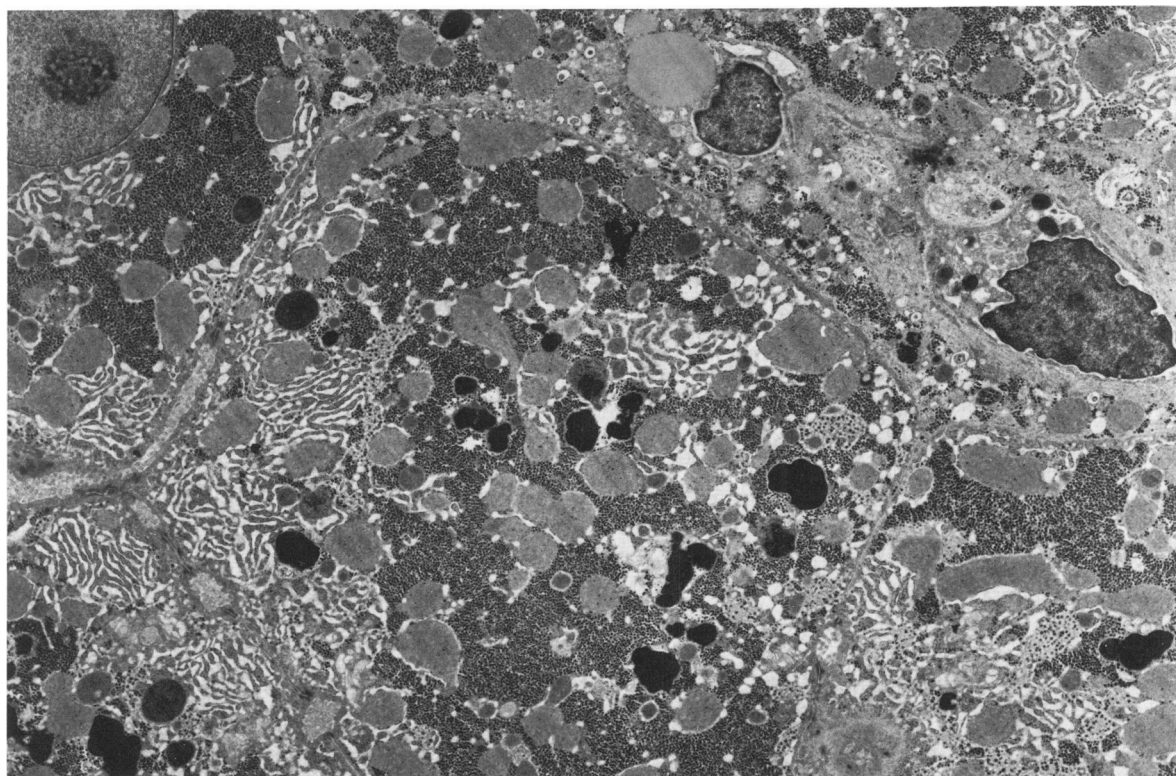


Figure 1—Electron micrograph of a liver biopsy specimen from a 2½-year-old Bedlington terrier. Hepatic copper was 6529 µg/g dry weight. Several large electron-dense bodies are evident. They are nonhomogeneous and single-membrane-limited. These bodies are probably lipolysosomes, and their distribution is random. (× 4500) We are indebted to Dr. S. S. Barham for this micrograph.

same basis—impaired biliary excretion of copper (Wilson's disease—Frommer;¹⁰ Bedlington disease—Su¹¹). Hepatic subcellular localization is different. In Wilson's disease it is in periportal hepatocytes, and in the Bedlington disease it is in the center of the lobules (Rappaport Zone 3)^{5,6} (Figure 2). In Wilson's disease copper accumulates in only 4 organs to any significant extent: liver, kidney, brain, and cornea. The affected Bedlingtons have elevated copper in the liver and kidney early and in the brain late,¹¹ but their corneas have not been studied. However, Kayser-Fleischer rings have not been seen in the dogs.^{1,8} Although the copper enzyme ceruloplasmin is very low in the plasma of over 90% of patients with Wilson's disease, it is normal in the dogs.¹¹ Urinary copper is increased in both diseases.¹¹ In both diseases there are hemostatic abnormalities.¹² However, only the affected dogs exhibit a platelet hypersensitivity to stimulation.¹³

The diagnosis is made in man if the patient has laboratory or clinical evidence of hepatic disease, clinical signs of lenticular or cerebellar disease, low serum ceruloplasmin, and hypercupriuria. When all or most of these are equivocal, copper assay of a liver biopsy specimen may be required to establish the diagnosis.

In the Bedlington disease only a liver biopsy and copper analysis can establish the diagnosis.

Penicillamine effectively removes the copper from the liver of the patient with Wilson's disease and apparently the Bedlington terrier with copper-loading as well.^{2,6}

Usefulness of the Model

The differences between the human and canine diseases (plasma ceruloplasmin, hepatic subcellular localization of copper, and platelet function) are outweighed by their remarkable similarities. The dog model should be useful in helping to discover the two most important problems of Wilson's disease: 1) Why cannot the liver excrete copper into the bile? and 2) Can pharmacologic agents reverse this etiologic defect? At present treatment is directed at removing copper from the patient via the urinary tract, a painfully slow process.

Availability

The Bedlington Terrier Club of America is actively seeking to isolate affected terriers so as to propagate

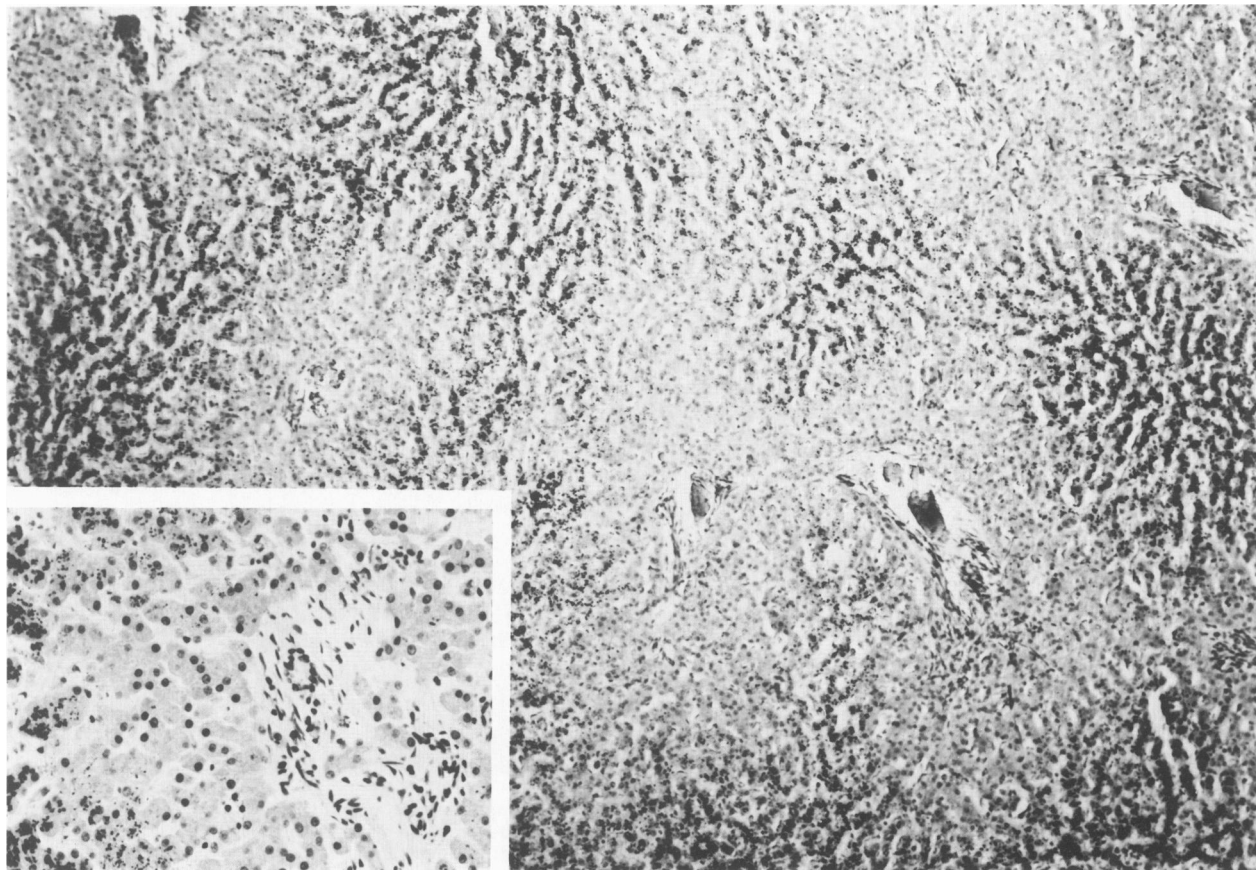


Figure 2—Photomicrograph of liver from a 1-year-old Bedlington terrier. The liver contained 1329 μg Cu/g dry weight. There is a striking accumulation of copper-containing granules in centrilobular and midzonal hepatocytes. ($\times 64$) **Inset**—Hepatocytes near the portal tract are virtually copper-free. (Rhodamine stain, $\times 250$)

only the unaffected dogs. Dogs with elevated hepatic copper may be available to investigators.

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